UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

May 20, 2011

MEMORANDUM

Subject:	Name of Pesticide Product:	INDOX2
	EPA Reg. No. /File Symbol:	773-OL
	DP Barcode:	DP 380196
	Decision No.:	436340
	Action Code:	R260
	PC Codes:	109701 (Permethrin: 42.50%)
		067710 (Indoxacarb: 13.01%)

From: Byron T. Backus, Ph.D., Toxicologist
Technical Review Branch
Registration Division (7505P)

Byron T. Backus
5/23/2011
M Hashim
T.L. TOXICOLOGY.

To: Autumn Metzger, RM 07
Insecticide-Rodenticide Branch
Registration Division (7505P)

Registrant: INTERVET, INC.

FORMULATION FROM LABEL:

Active Ingredient(s):	By wt.
067710 Indoxacarb	13.01%
109701 Permethrin	42.50%
Other Ingredient(s):	44.49%
TOTAL	100.00%

ACTION REQUESTED: The Risk Manager requests:

"Please review the attached companion animal safety studies, submitted in support of 773-OL, a new spot-on product containing indoxacarb and permethrin, to control fleas and ticks on dogs and puppies. Copies of the proposed label and CSF are also enclosed…"

BACKGROUND:

The material received includes two companion animal safety studies (an adult dog study in MRID 48135308 and a puppy study in MRID 48135309). Both studies were conducted on beagles. In addition, there is a copy of the proposed label and CSF (dated 6-16-10).

COMMENTS AND RECOMMENDATIONS:

1. An Agency contractor, Oak Ridge National Laboratory, conducted the primary reviews of the companion animal safety studies. TRB performed the secondary reviews and made changes as necessary.

2. In the adult beagle study (MRID 48135308) it was demonstrated that the test material, indoxacarb/permethrin (SCH 900560), had no adverse effects when administered to male and female adult beagles at 1x, 3x and 5x (reported as 0.1 mL/kg, 0.3 mL/kg, and 0.5 mL/kg, respectively) the dose of 0.1 mL/kg.

   The companion animal safety study in adult beagles (MRID 48135308) has been classified as **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200). This study does support the use of this formulation on adult dogs at a dosage rate of up to 0.1 mL/kg. However, it is noted that the 1x dosage study rate of 0.1 mL/kg is exceeded by the proposed application rates shown on the label (40-60 kg: 6.0 mL = 0.1 to 0.15 mL/kg; 20-40 kg: 4.0 mL = 0.1 to 0.2 mL/kg; 10-20 kg: 2.0 mL = 0.1 to 0.2 mL/kg; 5-10 kg: presumably 1.0 mL [the label gives 0.10 mL, but this is inconsistent with the dosages for the other weights] = 0.1 to 0.2 mL/kg; under 5 kg: 0.5 mL = 0.1 to 0.5 mL [for a 1 kg dog]). The dosage was inadequate to support a rate of 0.2 mL/kg (only a 2.5x safety margin).

   In addition, it is not understood how the incidence of "normal" Body Condition Score was calculated. For example (from p. 170 of MRID 48135308), in the 1x males 4 + 26 + 5 + 1 = 36 (which would indicate a BCS from 4/9 to 7/9 would be normal). However, among the control males the incidences for BCS 4/9 through 7/9 are 3 + 27 + 6 = 36, but "normal" occurred only 32 times.

3. In the puppy study in MRID 48135309 it was demonstrated that indoxacarb/permethrin (SCH 900560) had no adverse effects when applied at 2-week intervals to male and female 8 week old beagle puppies at 1x, 3x and 5x the dose of 0.1 mL/kg.

   This companion animal safety study in 8-week old puppies has been classified as **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200). However, the proposed label indicates the smallest amount of formulation in an applicator is 0.5 mL, while the puppies in this study initially weighed from 1.2 to 3.4 kg (which would mean a 1x dose level of from 0.12 to 0.34 mL). The registrant is going to have to address this inconsistency. In addition, only a dosage rate of up to 0.1 mL/kg is supported.

4. Refer to the attached DERs for additional comments.

DATA EVALUATION RECORD

INDOXACARB- PERMETHRIN (SCH 900560)
COMPANION ANIMAL SAFETY STUDY- Adult Beagles (OPPTS 870.7200)
MRID 48135308

Prepared for

Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
One Potomac Yard
2777 S. Crystal Drive
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Environmental Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831

Primary Reviewer:
Cheryl B. Bast, Ph.D., D.A.B.T.

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Date: NOV 24 2010

Secondary Reviewers:
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Robert H. Ross, M.S., Group Leader

Signature: Robert H Ross
Date: NOV 24 2010

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: L. A. Wilson
Date: NOV 24 2010

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT_Battelle, LLC., for the U.S. Department of Energy under Contract No. DE_AC05_00OR22725.

EPA Secondary Reviewer: Byron T, Backus, Ph.D. **Signature:** Byron T. Backus
Technical Review Branch, Registration Division (7505P) **Date:** 5/23/2011

EPA Tertiary Reviewer: Kit Farwell, D.V.M. **Signature:** KFarwell
Risk Assessment Branch VII, HED (7509P) **Date:** 5/23/2011

Template version 02/06

DATA EVALUATION RECORD

STUDY TYPE: Companion animal safety study- adult beagles; [OPPTS 870.7200]

PC CODES: 109701; 067710 **DP BARCODE:** 380196

TEST MATERIAL (PURITY): Indoxacarb (13.77 % w/w); Permethrin (43.48%, w/w)

SYNONYMS: SCH 900560

CITATION: Morse, Mark. (2010) Indoxacarb/Permethrin (SCH 900560): 10-week topical target animal safety study in adult beagles. Charles River Laboratories, 640 North Elizabeth Street, Spencerville, OH 45887. Study No. JTG00005 (Charles River Laboratories) and Intervet, Inc. Study No. 08267 (Sponsor). January 15, 2010. Unpublished. MRID 48135308.

SPONSOR: Intervet, Inc., 56 Livingston Ave., Roseland, NJ 07068

EXECUTIVE SUMMARY: In a companion animal safety study (MRID 48135308), six adult beagles/sex/group were administered a placebo control for SCH 900560 (≤0.03% w/w Indoxacarb and ≤0.06% w/w Permethrin; Lot No. 80911B) or SCH 900560 (13.77% w/w Indoxacarb and 43.48% w/w of Permethrin; Lot No. 80910B) by topical administration at 1x, 3x and 5x the recommended dose, every 2 weeks over a course of 10 weeks. The 1x dose was equivalent to 15 mg Indoxycarb/kg and 48 mg Permethrin/kg. The treatments were administered on days 0, 14, 28, 42, 56 and 70. Treatment-related effects were evaluated by monitoring for mortality or moribundity, cage side observations, clinical observations, body weight, food consumption, clinical pathology (hematology and clinical chemistry), urinalysis, fecal analysis, and application site observations.

All animals survived until scheduled sacrifice. There were no treatment-related effects on any parameter evaluated, including clinical observations, physical examination, body temperature, heart and respiratory rates, body weight, food consumption clinical chemistry, and hematology parameters, urinalysis, or fecal examination.

The study demonstrated that indoxacarb/permethrin (SCH 900560) had no effect when administered to male and female adult beagles at 1x, 3x and 5x the recommended dose.

This companion animal safety study in adult beagles is **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) with a dosage

rate of up to 0.1 mL/kg SCH 900560. The dosage was inadequate to support a rate of 0.2 mL/kg (only a 2.5x safety margin).

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided. The study was conducted according to GLP standards except the feed analysis, water analysis and analysis of contaminants in treats were not performed according to GLP regulations. However, these exceptions did not affect the quality of the study.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** SCH 900560 (Combination of Indoxacarb + Permethrin Topical Solution)

Description:	Pale, yellow liquid
Batch #:	Lot No. 80910B
Purity:	13.77% w/w Indoxacarb and 43.48% w/w Permethrin
Compound Stability:	Stable
CAS #:	Not provided

2. **Vehicle and/or positive control:** A placebo control of the spot-on formulation without active ingredient was used; ≤0.03% w/w of Indoxacarb and ≤0.06% w/w of Permethrin; Lot No. 80911B).

3. **Test animals:**

Species:	Dog	
Strain:	Beagle	
Age/weight at study initiation:	Adult- ~ 7 months old; Males: 6.6 – 8.9 kg and Females: 5.9 – 7.3 kg	
Source:	Marshall BioResources, North Rose, NY	
Housing:	Dogs were housed individnally in suspended stainless steel cages.	
Diet:	PMI Nutrition International Certified Canine Diet® #5007. Dogs were given a 400-gram ration of food daily. Food was made available for 4 hours each day and then removed from each cage. Each dog was offered a certified K-9 beef treat once on Monday, Wednesday, and Friday for positive reinforeement.	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	64-84 °F
	Humidity:	30-70%
	Air changes:	10 or more air changes/hour
	Photoperiod:	12 hrs light/12 hrs dark
Acclimation period:	~ 11 days	

B. STUDY DESIGN:

1. **In life dates:** Start: December 29, 2008; End: March 23, 2009

2. **Animal assignment:** Twenty four dogs of each sex were chosen for the study and weighed. A standard block randomization procedure was used to assign the dogs by weight to the control and treatment groups. Dogs assigned had body weight within ± 18% of the mean body weight for each sex. See Table 1.

TABLE 1. Study design[a]

Test Group	Number of dogs		Dose material	Dose level	Indoxacarb dose (mg/kg)	Permethrin dose (mg/kg)	Dose volume (mL/kg)
	Males	Females					
1	6	6	Control (vehicle)	0x	0	0	0.5
2	6	6	Indoxacarb/permethrin	1x	15	48	0.1
3	6	6	Indoxacarb/permethrin	3x	45	144	0.3
4	6	6	Indoxacarb/permethrin	5x	75	240	0.5

[a] Data from p. 22, Section 8.3 in MRID 48135308.

3. **Dose selection rationale**: The dose levels were selected based on information provided by the Sponsor and on regulatory guidelines on target animal safety studies.

4. **Preparation and treatment**: The dose levels for the treated groups were 1x, 3x and 5x SCH 900560 at dose volumes of 0.1, 0.3 and 0.5 mL/kg, respectively. The placebo control was administered at a dose volume of 0.5 mL/kg. The test article was taken from its blister pack and transferred into a vial. A plastic syringe (no needle or cannula) was then used to draw up the appropriate dose. Animals were not shaved prior to administration and the test article or control was administered topically directly to the epidermis along the dorsal mid-line by first parting the hair between the shoulder blades. For the higher doses, the application was extended along the dorsal mid-line to avoid run-off.

5. **Statistics**: Data for each sex within a set were analyzed separately. All continuous variables were analyzed statistically by repeated measures analysis of variance (RMANOVA).

   Statistical analysis was performed for the following parameters: body weight, food consumption, body temperature, heart rate, respiratory rate, hematology (except for blood smear data), serum chemistry, coagulation and urinalysis (pH and specific gravity only). All pair-wise comparisons of active treatment groups with the control were tested at the 0.10 significance level.

C. METHODS:

1. Observations

a. **General health observations**: General health/mortality and moribundity checks were performed twice daily and cage-side observations performed each morning beginning upon the receipt of the dogs. Detailed clinical observations were performed twice daily at least 6 hours apart starting on day -7. On treatment days, dogs were observed prior to dosing and detailed observations were performed hourly for at least four hours post-dosing. The immediate post-dose observation was recorded for at least 15 minutes but up to 1 hour by the person administering the test material. After this point, blinded personnel performed the detailed clinical observations. Dogs were assessed for any

clinical signs of toxicity in the following parameters (although the list was not limited to these only): general health, behavior, equilibrium/coordination, eyes, ears, nose, oral cavity, thorax, skin and fur, limbs and feet, abdomen, external genitalia, vomiting, diarrhea, mucous membranes, cardiovascular, respiratory, and central nervous systems.

b. **Clinical assessments**: Detailed physical examinations were performed by the veterinary staff on study days -7, -3, 15, 29, 71 and 84. The clinical assessments included evaluation of the following: general condition/behavior, equilibrium/coordination, neurological system, general ocular (no ophthalmoscope), integument, musculoskeletal, gastrointestinal, cardiovascular and respiratory systems, conditions/color of mucous membranes and body temperature. Also assessed were Body Condition Scores (BCS) graded on a 9-point scale where 1/9 was emaciated and 9/9 was obese.

Migration of the test/control substance was evaluated during the first hour post-dosing on days 0, 14, 28, 42, 56 and 70. The following migration scores were used: 0= no migration- the test material did not migrate past the point of application; 1= slight migration- the test material migrated from the point of application but did not drip off the animal and 2= moderate migration- the test material had the potential to or did actually drip off the animal.

2. **Body weight**: Body weight was recorded on the following study days: -7, -3, 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, and 84.

3. **Food and water consumption**: Food consumption was measured and recorded daily starting on day -7. Food was offered for four hours per day. On dosing days, the animals were fed prior to dosing. Water consumption was not recorded.

4. **Hematology & Clinical Chemistry**: Blood was collected for hematology and clinical chemistry assessments on all dogs on days -7, -1, 15, 29, 71, and 77. Animals were fasted (food only) overnight prior to blood collection. Blood samples were collected from the jugular vein. The CHECKED (X) parameters were examined.

a. **Hematology**

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count	X	Reticulocyte count (Absolute and %)
	Blood clotting measurements*	X	Large unstained cells (LUC)
X	(Thromboplastin time)		Fibrinogen
	(Clotting time)	X	Heinz bodies (%)
X	(Prothrombin time)		Mean platelet volume (MVP)

* Recommended for companion animals safety evaluation based on OPPTS 870.7200

b. **Clinical Chemistry**

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Creatinine*
	Sodium/Potassium ratio	X	Urea nitrogen*
X	Phosphorus *	X	Total Cholesterol
X	Potassium* (K)	X	Globulins*
X	Sodium* (NA)	X	Glucose*
	ENZYMES (more than 2 hepatic enzymes, eg.,)	X	Total bilirubin *
X	Alkaline phosphatase (AP)*	X	Total protein*
	Cholinesterase (ChE)	X	Triglycerides
	Creatine phosphokinase	X	Albumin/Globulin ratio
	Lactic acid dehydrogenase (LDH)	X	Direct bilirubin*
X	Alanine aminotransferase (ALT/also SGPT)*		Indirect bilirubin
X	Aspartate aminotransferase (AST/also SGOT)*		BUN/Creatinine ratio
X	Gamma glutamyl transferase (GGT)		TCO_2 Bicarbonate
	Glutamate dehydrogenase		Amylase
	Sorbitol dehydrogenase		Lipase

*Recommended for a companion animal safety evaluation based on OPPTS 870.7200

5. **Urinalysis:** Urine was collected for assessment on all dogs on days -7, -1, 15, 29, 71, and 77. Urine was collected by cage pan drainage overnight. The parameters evaluated are included below.

X	Appearance (color/clarity)	X	Glucose
X	Volume	X	Ketones
X	Specific gravity / osmolality	X	Bilirubin
X	pH	X	Blood/ red blood cells
	Sediment (microscopic)		Nitrate
X	Protein	X	Urobilinogen

6. **Fecal samples:** Fecal samples were collected on the following study days: -17 to -15, -7, -1, 15, 29, 71, and 77 and observed for color and consistency. Parasite evaluation was performed by floatation.

7. **Sacrifice and Pathology**: On study Day 84, all dogs were euthanized by intravenous (i.v.) injection of a lethal dose of sodium pentobarbital. No tissue collection was performed, and carcasses were discarded. It is noted that the 870.7200 Guidelines state that routine sacrifice or necropsy is not required for surviving animals.

II. RESULTS

A. OBSERVATIONS:

1. **Clinical signs of toxicity**: There were no treatment-related effects. Incidental signs observed at all doses and in the control group included soft and/or mucoid stools, hair

loss, red/swollen pinnae, reddened areas, salivation, no feces, few feces, colored mucoid material in the cage/tray, scabs, vomitus, diarrhea, ocular discharge, and cracked footpads. Because none of the signs were observed in a dose-dependent manner and all were sporadic, they were not considered treatment-related.

Some statistical differences in body temperature were observed in treated dogs during the study. However, they were sporadic, of small magnitude, and lacked a dose-response relationship. Therefore, they were not considered treatment-related.

Some dogs had higher respiratory rates (100 to 170 breaths per minute) on day 84; however, because control and treated animals were similarly affected, this effect was considered incidental to treatment. (Incidence was one control male and one control female; one 1X group female; and two 5X group females).

Other sporadic incidental findings were as follows: salivation in one control male, one 1X female, and one 5X female on day 29; and low respiratory rate (10 breaths per minute) in one control female on day 71. These effects are considered incidental to treatment.

Body Condition Scores (BCS) (Table 2), graded on a 9-point scale, (1/9 is an emaciated dog with obvious loss of muscle mass and 9/9 is an obese dog) ranged from 4/9 to 7/9 for males and 3/9 to 7/9 for females.

TABLE 2. Summary of Body Condition Scores (total observations/animals affected) in dogs on study days -18 to 84[a]

Parameter	Control	1x	3x	5x
Males				
General condition				
Normal	32/6	36/6	36/6	35/6
BCS 4/9	3/2	4/2	2/2	1/1
BCS 5/9	27/6	26/6	20/6	25/6
BCS 6/9	6/5	5/4	13/6	5/4
BCS 7/9	0/0	1/1	1/1	5/4
Females				
General condition				
Normal	35/6	31/6	34/6	35/6
BCS 3/9	1/1	0/0	0/0	0/0
BCS 4/9	9/3	10/4	4/2	3/2
BCS 5/9	19/6	20/6	21/6	26/6
BCS 6/9	5/5	5/4	9/5	7/4
BCS 7/9	2/2	1/1	2/1	0/0

[a]Data from Table 3, pp. 170-174 in MRID 48135308

[b] BCS= body condition score with 1/9 being emaciated and 9/9 being obese

It is not understood how the incidence of "normal" was calculated. For example, in the 1x males 4 + 26 + 5 + 1 = 36 (which would indicate a BCS from 4/9 to 7/9 would be normal. However, among the control males the incidences for BCS 4/9 through 7/9 are 3 + 27 + 6 = 36, but normal occurred only 32 times.

2. **Cosmetic effects**: Very little migration of the test substance/control occurred. Most animals scored a 0 (no migration). A score of 1 (slight migration) was observed in several animals as follows: one 3X male and one 5X male on day 56; one 5X females on day 42, and one 5X female on days 56 and 70. A score of 2 (moderate migration) was given to one male and one female control on day 70; while the material migrated, it did not actually drip off of the dog.

3. **Mortality**: There were no treatment-related deaths. All dogs survived until the termination of the study.

B. **BODY WEIGHT AND WEIGHT GAIN**: Select mean body weight data are presented in Table 3. No biologically significant treatment-related changes in mean body weight or body weight gain were observed. A statistically significant decrease in mean body weight was noted in 1X dogs compared to controls when pooled by sex and time. In the absence of a dose-response relationship, and given that all groups generally gained weight at comparable rates, this was considered incidental to treatment.

TABLE 3. Mean body weight (g ± S.D.) in dogs[a]

Day	Control	1x	3x	5x
Males				
0	7450 ± 238.7	7602 ± 1017.6	7595 ± 533.3	7768 ± 477.0
21	7943 ± 246.4	7994 ± 1137.9	8167 ± 681.8	8175 ± 496.3
42	8129 ± 369.3	8175 ± 1229.9	8402 ± 731.7	8603 ± 445.1
63	8725 ± 292.7	8690 ± 1490.2	8859 ± 756.7	9117 ± 461.8
84	8750 ± 258.5	8731 ± 1213.1	8941 ± 813.0	9207 ± 368.4
Females				
0	6496 ± 303.1	6703 ± 478.1	6885± 427.3	6806 ± 363.1
21	6884 ± 397.8	6970 ± 484.5	7255 ± 642.2	7209 ± 452.1
42	6916 ± 500.6	7013 ± 385.8	7451 ± 803.0	7365 ± 622.2
63	7480 ± 582.8	7348 ± 533.3	8023 ± 691.0	7899 ± 561.0
84	7528 ± 521.6	7390 ± 489.2	8128 ± 711.4	7928 ± 585.2

[a]Data from Table 5, pp. 182-189 in MRID 48135308

C. **FOOD CONSUMPTION:** No significant treatment-related findings were observed in any dogs. Throughout the study, the treated dogs ate similar amounts to the control dogs. Select food consumption data are provided in Table 4.

TABLE 4. Mean food consumption (g/animal/day ± SD) in dogs[a]

Week	Control	1x	3x	5x
Males				
3	256 ± 37.6	292 ± 41.9	259 ± 41.9	266 ± 30.1
6	313 ± 22.6	302 ± 31.7	291 ± 34.1	309 ± 32.5
9	284 ± 48.3	306 ± 27.8	259 ± 39.6	272 ± 46.4
12	276 ± 80.7	287 ± 89.7	280 ± 85.8	300 ± 70.4
Females				
3	234 ± 39.6	252 ± 54.0	266 ± 26.6	255 ± 35.0
6	280 ± 44.7	286 ± 51.1	304 ± 44.8	288 ± 35.0
9	252 ± 55.9	261 ± 41.2	276 ± 39.1	267 ± 50.3
12	241 ± 69.1	242 ± 84.1	257 ± 45.4	280 ± 63.0

[a]Data from Table 7, pp. 200-207 in MRID 48135308

D. BLOOD ANALYSES:

1. **Hematology**: There were no treatment-related effects in any hematology or coagulation parameters. Occasional statistically significant differences were observed but they were minor in magnitude, lacked a dose-response relationship, and mean values were generally in the range of historical control values. Therefore, they were considered incidental to treatment.

2. **Clinical chemistry**: There were no treatment-related effects in any clinical chemistry parameters. Occasional statistically significant differences were observed but they were minor in magnitude, lacked a dose-response relationship, and mean values were generally in the range of historical control values. Therefore, they were considered incidental to treatment.

3. **Urinalysis:** There were no treatment-related findings observed in the urinalysis parameters evaluated. Some statistically significant differences were observed in specific gravity. However, because the findings were sporadic and lacked a dose-response or time-dependent relationship, they were considered incidental to treatment.

4. **Fecal examination**: There were no treatment-related findings in fecal parameters, and there were no findings of parasites in any fecal samples.

E. PATHOLOGY RESULTS:

No pathological assessment was performed.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: The study author concluded that the administration of Indoxacarb/Permethrin Topical Solution (SCH 900560) was well-tolerated in adult Beagle dogs at dosage levels of 1x, 3x, or 5x; the packaged dose was described as 15 mg Indoxacarb and 48 mg Permethrin per kg of body weight. No adverse test article-related effects were noted in either male or female dogs.

B. REVIEWER COMMENTS: The reviewer agrees with the study author that no adverse effects were observed in dogs in any treatment group. All animals survived until scheduled sacrifice. There were no treatment-related effects on any parameter evaluated, including clinical observations, physical examination, body temperature, heart and respiratory rates, body weight, food consumption clinical chemistry and hematology parameters, urinalysis, or fecal examination. Although there were some statistically significant differences in some of these parameters, none exhibited a dose-response relationship or were consistent throughout the study. Therefore, the sporadic effects are considered incidental to treatment and biologically irrelevant. This study does support the use of this formulation on adult dogs at a dosage rate of 0.1 mL/kg. However, it is noted that the 1x dosage study rate of 0.1 mL/kg is exceeded by the proposed application rates shown on the label (40-60 kg: 6.0 mL = 0.1 to 0.15 mL/kg; 20-40 kg: 4.0 mL = 0.1 to 0.2 mL/kg; 10-20 kg: 2.0 mL = 0.1 to 0.2 mL/kg; 5-

10 kg: presumably 1.0 mL [the label gives 0.10 mL, but this is inconsistent with the dosages for the other weights] = 0.1 to 0.2 mL/kg; under 5 kg: 0.5 mL = 0.1 to 0.5 mL [for a 1 kg dog]).

This companion animal safety study in adult beagles is **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) with a 1x dosage rate of up to 0.1 mL/kg. The dosage was inadequate to support a rate of 0.2 mL/kg (only a 2.5x safety margin).

C. **STUDY DEFICIENCIES:** The 1x dosage rate should have been at least 0.2 mL/kg. In addition, it is not understood how the incidence of "normal" Body Condition Score was calculated. For example, in the 1x males 4 + 26 + 5 + 1 = 36 (which would indicate a BCS from 4/9 to 7/9 would be normal). However, among the control males the incidences for BCS 4/9 through 7/9 are 3 + 27 + 6 = 36, but "normal" occurred only 32 times.

DATA EVALUATION RECORD

INDOXACARB- PERMETHRIN (SCH 900560)
COMPANION ANIMAL SAFETY STUDY- BEAGLE PUPPIES (OPPTS 870.7200)
MRID 48135309

Prepared for

Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
One Potomac Yard
2777 S. Crystal Drive
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Environmental Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831

Primary Reviewer:
Dana F. Glass, D.V.M.

Signature: Dana F Glass
Date: DEC 06 2010

Secondary Reviewers:
Cheryl B. Bast, Ph.D., D.A.B.T.

Signature: Cheryl B Bast
Date: DEC 06 2010

Robert H. Ross, M.S., Group Leader

Signature:
Date: DEC 06 2010

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: L.A. Wilson
Date: DEC 06 2010

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT_Battelle, LLC., for the U.S. Department of Energy under Contract No. DE_AC05_00OR22725.

EPA Secondary Reviewer: Byron T, Backus, Ph.D. **Signature:** Byron T. Backus
Technical Review Branch, Registration Division (7505P) **Date:** 5/23/2011

EPA Tertiary Reviewer: Kit Farwell, D.V.M. **Signature:** Kit Farwell
Risk Assessment Branch VII, HED (7509P) **Date:** 5/23/2011

Template version 02/06

DATA EVALUATION RECORD

STUDY TYPE: Companion animal safety study- beagle puppies; [OPPTS 870.7200]

PC CODES: 109701; 067710 **DP BARCODE:** 380196

TEST MATERIAL (PURITY): Indoxacarb (13.77 % w/w); Permethrin (43.48%, w/w)

SYNONYMS: SCH 900560

CITATION: Morse, Mark. (2010) Indoxacarb/Permethrin: 10-week topical target animal safety study in Beagle puppies. Charles River Laboratories, 640 North Elizabeth Street, Spencerville, OH 45887. Study No. JTG00004 (Charles River Laboratories) and Schering-Plough Study No. 08266 (Sponsor). January 15, 2010. Unpublished. MRID 48135309.

SPONSOR: Intervet, Inc., Roseland, NJ 07068

EXECUTIVE SUMMARY: In a companion animal safety study (MRID 48135309), six 8-week old beagle puppies/sex/group were administered either a placebo control for SCH 900560 (≤0.06% w/w of both Indoxacarb and Permethrin; Lot No. 80911B) or SCH 900560 (13.77% w/w of Indoxacarb and 43.48% w/w of Permethrin; Lot No. 80910B) by topical administration at 1x, 3x and 5x the recommended dose every 2 weeks over a course of 10 weeks. The 1x dose was equivalent to 15 mg Indoxacarb/kg and 48 mg Permethrin/kg. The treatments were administered on days 0, 14, 28, 42, 56 and 70. Treatment-related effects were evaluated by monitoring mortality, moribundity, cage side observations, clinical observations, body weight, food consumption, clinical pathology (hematology and clinical chemistry), urinalysis and dose site observations. A complete necropsy and histopathological examination was performed on one puppy euthanized moribund.

There were no treatment-related effects on survival, clinical signs, body weight, body weight gain, food consumption, clinical chemistry and hematology parameters, urinalysis or gross examination at necropsy. One male puppy in the 1x group was euthanized on study day 37 due to failure to thrive but an exact cause of death was not determined even with extensive gross and histopathological examination. As this was the only death and there was not a determined cause, it was not considered treatment-related. Upon application of the test material, one pup at 5x had a migration score of 2 (moderate migration), although the test material was not observed to be dripping off the dog. No specific treatment-related signs of irritation were observed on the application site of any puppies. Several control and treated puppies displayed carpal enlargement of the forelimb with some inward rotation; therefore, a few of these dogs were randomly selected

for thorough histopathological examination of the carpal joint. No accompanying histopathological findings were identified. The study author stated that the food administered to the puppies was a high-performance food designed for adult dogs and could have been the cause of the deformity. This was not considered a treatment-related effect.

The study demonstrated that indoxacarb/permethrin (SCH 900560) had no adverse effects when applied at 2-week intervals to male and female 8 week old beagle puppies at 1x, 3x and 5x the recommended dose of 0.1 mL/kg.

This companion animal safety study in 8-week old puppies is **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) with a 1x dosage rate of up to 0.1 mL/kg. However, the proposed label indicates the smallest amount of formulation in an applicator is 0.5 mL, while the puppies in this study initially weighed from 1.2 to 3.4 kg (which would mean a 1x dose level of from 0.12 to 0.34 mL). The registrant is going to have to address this inconsistency.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided. The study was conducted according to GLP standards except the feed analysis, water analysis and analysis of contaminants in treats were not performed according to GLP regulations. However, these exceptions did not affect the quality of the study.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** SCH 900560 (Combination of Indoxacarb + Permethrin Topical Solution)

Description:	Pale, yellow liquid
Batch #:	Lot No. 80910B
Purity:	13.77% w/w Indoxacarb and 43.48% w/w Permethrin
Compound Stability:	Stable
CAS #:	Not provided

2. **Vehicle and/or positive control:** A placebo control of the spot-on formulation without active ingredient was used (≤0. 06% w/w of each compound; Lot No. 80911B).

3. **Test animals:**

Species:	Dog
Strain:	Beagle
Age/weight at study initiation:	Puppies- ~ 8 weeks old; Males: 1.6 – 3.4 kg and Females: 1.2 – 2.5 kg
Source:	Marshall BioResources, North Rose, NY
Housing:	Puppies were housed together (2 males or 2 females per cage) for at least the first 3 weeks of dosing and then kept individually. All were kept in suspended stainless steel cages.

Diet:	Iams Eukanuba Active Performance 28/18, premium performance formula. Dogs were fed food moistened with tap water three times daily during acclimation which was eventually changed to dry food only being left in the cage overnight as the puppies became older. During dosing, 1/4th of a certified K-9 beef treat was given once daily for positive reinforcement.	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	64-74 °F
	Humidity:	26-58%
	Air changes:	10 or more air changes/hour
	Photoperiod:	12 hrs light/12 hrs dark
Acclimation period:	~ 7 days	

B. STUDY DESIGN:

1. **In life dates:** Start: January 1, 2009 (Day 0: first application of test material); End: March 30, 2009

2. **Animal assignment:** Twenty four puppies of each sex were chosen for the study and weighed. A standard block randomization procedure was used to assign the dogs by weight to the control and treatment groups. Puppies assigned had body weight within ± 50% of the mean body weight for each sex. Table one provides the study design, and Table two gives the puppy ages on Day 0.

TABLE 1. Study design[a]

Test Group	Number of dogs		Dose material	Dose level	Indoxacarb dose (mg/kg)	Permethrin dose (mg/kg)	Dose volume (mL/kg)
	Males	Females					
1	6	6	Control (vehicle)	0x	0	0	0.5
2	6	6	Indoxacarb/permethrin	1x	15	48	0.1
3	6	6	Indoxacarb/permethrin	3x	45	144	0.3
4	6	6	Indoxacarb/permethrin	5x	75	240	0.5

[a] Data from p. 27, Section 9.3 in MRID 48135309

TABLE 2. Puppy Ages on Day 0[a]

Test Group	Age Range (Days)		Mean Age (Days) ± S.D.	
	Males	Females	Males	Females
1	52-59	52-60	54.83 ± 2.40	55.17 ± 2.86
2	52-60	52-60	56.50 ± 3.33	55.33 ± 3.27
3	52-60	52-59	57.00 ± 2.97	56.17 ± 2.71
4	54-59	52-60	55.67 ± 2.25	55.00 ± 3.29

[a] Data calculated from information on p. 552 in MRID 48135309

3. **Dose selection rationale**: The dose levels were selected based on information provided by the Sponsor and on regulatory guidelines on target animal safety studies.

4. **Preparation and treatment**: The dose levels for the treated groups were 1x, 3x and 5x SCH 900560 at dose volumes of 0.1, 0.3 and 0.5 mL/kg, respectively. The placebo control was administered at a dose volume of 0.5 mL/kg. The test article was taken from its blister pack and transferred into a vial. A plastic syringe (no needle or cannula) was then used to draw up the appropriate dose. Animals were not shaved prior to administration and the test article or

control was administered topically directly to the epidermis along the dorsal mid-line by first parting the hair between the shoulder blades. For the higher doses, the application was extended along the dorsal mid-line to avoid run-off.

5. **Statistics**: All statistical comparisons of effects and 'treatment by time', 'treatment by sex' or 'treatment by time by sex' interactions were performed at the 0.1 level of significance using SAS PROC MIXED Version 9.1. All continuous variables were analyzed using a mixed model and ordinal variables were analyzed using contingency table analysis.

   Statistical analysis was performed for the following parameters: body weight, food consumption, body temperature, heart rate, respiratory rate, hematology (except for blood smear data), serum chemistry, coagulation and urinalysis (pH and specific gravity only).

C. METHODS:

1. Observations

a. General health observations: General health/mortality and moribundity checks were performed twice daily and cage-side observations performed each morning, beginning the day dogs were received. Detailed clinical observations were performed twice daily at least 6 hours apart starting on day -7. On treatment days, dogs were observed prior to dosing and detailed observations were performed hourly for at least four hours post-dosing. The immediate post-dose observation was recorded for at least 15 minutes but up to 1 hour, as required, by the person administering the test material. After this point, blinded personnel performed the detailed clinical observations. Puppies were assessed for any clinical signs of toxicity in the following parameters, although the list was not limited to these only: general health, behavior, equilibrium/coordination, changes in skin and hair, eyes and mucous membranes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs and feet, vomiting, diarrhea, cardiovascular, respiratory, circulatory, and central nervous systems.

b. Clinical assessments: Detailed physical examinations were performed by the veterinary staff on study days -6, -1, 15, 29, 71 and 84. The clinical assessments included evaluation of the following: general condition/behavior, equilibrium/coordination, neurological system, general ocular (no ophthalmoscope), integument, musculoskeletal, gastrointestinal, cardiovascular and respiratory systems, condition/color of mucous membranes and body temperature. Body Condition Scores (BCS) were also determined graded on a 9-point scale where 1/9 was emaciated and 9/9 was obese.

Migration of the test/control substance was evaluated post-dosing on days 0, 14, 28, 42, 56 and 70 during the first hour. The following migration scores were used: 0= no migration- the test material did not migrate past the point of application; 1= slight migration- the test material migrated from the point of application but did not drip off the animal and 2= moderate migration- the test material had the potential or did actually drip off the animal.

2. **Body weight**: Body weight was recorded on the following study days: -13, -12, -11, -10, -9, -8, -7, -4, -1, 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84 and 88.

3. **Food and water consumption**: Food consumption was measured and recorded daily starting on day -7. For day -7 to day 20, food consumption was recorded on pair-housed animals. Food was offered for two to four hours per day as the pups became older and on the day of dosing, pups were fed prior to dosing. Water consumption was not recorded.

4. **Hematology & Clinical Chemistry**: Blood was collected for hematology and clinical chemistry assessments on all dogs on days -6, 15, 29, 71, 77 and prior to euthanasia. Animals were fasted (food only) overnight prior to blood collection. Blood samples were collected from the jugular vein. The CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count	X	Reticulocyte count (Absolute and %)
	Blood clotting measurements*	X	Large unstained cells (LUC)
X	(Thromboplastin time)		Fibrinogen
	(Clotting time)	X	Heinz bodies (%)
X	(Prothrombin time)		Mean platelet volume (MVP)

* Reeommended for companion animals safety evaluation based on OPPTS 870.7200

b. Clinical Chemistry

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Creatinine*
	Sodium/Potassium ratio	X	Urea nitrogen*
X	Phosphorus *	X	Total Cholesterol
X	Potassium* (K)	X	Globulins*
X	Sodium* (NA)	X	Glucose*
	ENZYMES (more than 2 hepatic enzymes, eg.,)	X	Total bilirubin *
X	Alkaline phosphatase (AP)*	X	Total protein*
	Cholinesterase (ChE)	X	Triglycerides
	Creatine phosphokinase	X	Albumin/Globulin ratio
	Lactic acid dehydrogenase (LDH)	X	Direct bilirubin*
X	Alanine aminotransferase (ALT/also SGPT)*		Indirect bilirubin
X	Aspartate aminotransferase (AST/also SGOT)*		BUN/Creatinine ratio
X	Gamma glutamyl transferase (GGT)		TCO_2 Bicarbonate
	Glutamate dehydrogenase		Amylase
	Sorbitol dehydrogenase		Lipase

*Recommended for a companion animal safety evaluation based on OPPTS 870.7200

5. **Urinalysis:** Urine was collected for assessment on all dogs on day -6, 15, 29, 71, 77 and prior to euthanasia. Urine was collected by cage pan drainage overnight except for the sample obtained at euthanasia which was collected by cystocentesis. The parameters evaluated are included below.

X	Appearance (color/clarity)	X	Glucose
X	Volume	X	Ketones
X	Specific gravity / osmolality	X	Bilirubin
X	pH	X	Blood/ red blood cells
	Sediment (microscopic)		Nitrate
X	Protein	X	Urobilinogen

6. **Fecal samples:** Fecal samples were collected on the following study days: day after arrival to lab, -6, 15, 29, 71, and 77 and observed for color and consistency. Parasite evaluation was performed by floatation.

7. **Sacrifice and Pathology**: The following tables are provided to describe the terminal procedures. Most dogs underwent gross examination and tissues were collected; however, one dog had complete histopathology performed. It is noted that the 870.7200 Guidelines state that routine sacrifice or necropsy is not required for surviving animals.

TABLE 3. Terminal procedures performed on puppies[a]

Group No.	No. males/no. females	Scheduled day of euthanasia	Terminal procedures		Histopathology
			Gross necropsy[b]	Tissue collection	
1	4/3	88	x	x	Limited
2	5/4	88	x	x	Limited[c]
3	4/3	88	x	x	Limited
4	5/3	88	x	x	Limited
Unscheduled euthanasia animal			x	x	Full

[a] Data from table on p. 33, Section 10.10 in MRID 48135309

[b] At least 3 animals/sex/group were selected for partial gross examination, which included all of the puppies that had carpal joint abnormalities noted clinically, for any remaining slots, the animals were selected randomly. The partial necropsy included selected tissue collection and subsequent histopathological examination of the radiocarpal joint.

[c] One Group 2 male was euthanized moribund on study day 37 and subjected to complete necropsy and histopathological examination of an extensive set of tissues (see table below).

The following tissues (checked with X below) were collected from the animal euthanized moribund and preserved in 10% neutral buffered formalin except for the eyes which were fixed in Davidson's fixative before being transferred to neutral buffered formalin.

X	DIGESTIVE SYSTEM	X	CARDIOVASCULAR/ HEMATOLOGY	X	NEUROLOGIC
X	Tongue	X	Aorta	X	Brain
X	Salivary glands	X	Heart	X	Peripheral nerve
X	Esophagus	X	Bone marrow (sternum/femur)	X	Spinal cord (3 levels)
X	Stomach	X	Lymph nodes	X	Pituitary
X	Duodenum	X	Spleen	X	Eyes (optic nerve)
X	Jejunum	X	Thymus	**X**	**GLANDULAR**
X	Ileum	X	Bone marrow smear	X	Adrenal gland
X	Cecum	**X**	**UROGENITAL**	X	Lacrimal gland
X	Colon	X	Kidneys	X	Parathyroid
X	Rectum	X	Urinary bladder	X	Thyroid
X	Liver	X	Testes	**X**	**OTHER**
X	Gall bladder	X	Epididymides	X	Bone (sternum and/or femur)
	Bile duct (rat)	X	Prostate	X	Skeletal muscle
X	Pancreas		Seminal vesicles	X	Skin (site of application)
X	**RESPIRATORY**		Ovaries	X	All gross lesions and masses
X	Trachea		Uterus	X	Animal identification (ear tattoo)
X	Lung		Mammary gland		
	Nose				
X	Nasal turbinates				
X	Pharynx				
X	Larynx				

II. RESULTS

A. OBSERVATIONS:

1. **Clinical signs of toxicity**: Select physical observations are provided in Table 3. On study day 37 one male puppy in the 1x group was found laterally recumbent, cool to the touch with labored breathing, pale mucous membranes and hemorrhagic feces, and was euthanized. Some puppies, treated and controls, early in the study showed signs of muscle wasting and low body condition scores. This was diagnosed as Fading Puppy Syndrome and supplemental nutrition was started. Over time, these puppies responded and began to thrive and gain weight. Later in the dosing period (study days 71-84), puppies in all dose groups, including some controls, had enlargement of the carpal areas with some mild, bilateral angular deformity of the forelimbs. There was a slightly higher incidence in the puppies of the 1x group. The study authors stated that the food administered to the puppies may have contributed to this condition as it was found to be a high performance food recommended for adult dogs. Clinical chemistry results did not indicate any changes in calcium or phosphorus which could support a nutritional secondary hyperthyroidism and there were no accompanying histopathological findings of the carpal joint. Other signs observed at all doses and in the control group included soft and/or mucoid stools, diarrhea, scabs, hair loss,

and ocular discharges. As none of the signs were observed in a dose-dependent manner and were sporadic, they were not considered treatment-related. Some statistically differences were observed in treated pups on body temperature and respiration rate, however, they were sporadic and did not indicate a dose response and were not considered treatment-related.

TABLE 4. Summary of select physical examination parameters (total observations/animals affected) in puppies on study days -14 to 88[a]

Parameter	Control	1x	3x	5x
Males				
General condition				
Normal	36/6	34/6	36/6	36/6
BCS 2/9[b]	1/1	0/0	0/0	0/0
BCS 3/9	1/1	2/2	0/0	1/1
BCS 4/9	6/3	7/4	1/1	7/3
BCS 5/9	13/5	15/6	14/5	18/6
BCS 6/9	12/6	9/4	18/6	10/5
BCS 7/9	3/2	1/1	3/2	0/0
Musculoskeletal				
Normal	30/6	27/6	29/6	28/6
Carpal jt enlargement	3/3	5/4	4/3	6/5
Toes turned inward	3/2	3/2	5/3	4/2
Distal leg turns inward	0/0	1/1	0/0	0/0
Skin				
Normal	32/6	27/6	33/6	29/6
Raised red areas	1/1	3/2	1/1	2/2
Scabs	1/1	5/3	2/2	3/3
Hair loss	0/0	1/1	1/1	2/2
Abrasion	1/1	0/0	0/0	0/0
Females				
General condition				
Normal	36/6	35/6	36/6	34/6
BCS 2/9	1/1	0/0	0/0	1/1
BCS 3/9	2/1	1/1	0/0	4/2
BCS 4/9	14/6	7/6	10/4	5/5
BCS 5/9	10/4	16/6	17/6	15/6
BCS 6/9	8/3	12/6	9/5	11/6
BCS 7/9	1/1	0/0	0/0	0/0
Musculoskeletal				
Normal	35/6	29/6	32/6	33/6
Carpal jt enlargement	0/0	2/2	0/0	1/1
Toes turned inward	0/0	4/3	4/3	1/1
Distal leg turns inward	0/0	1/1	0/0	0/0
Skin				
Normal	27/6	30/6	30/6	28/6
Raised red areas	3/3	3/3	3/3	5/5
Scabs	4/3	1/1	3/3	3/2
Hair loss	1/1	0/0	0/0	2/2
Abrasion	NR	NR	NR	NR

[a]Data from Table 5, pp. 196-202 in MRID 48135309.

[b] BCS= body condition score with 1/9 being emaciated and 9/9 being obese

NR= not reported

2. **Cosmetic effects**: Very little migration of the test substance/control occurred. Most animals scored a 0 (no migration). A score of 1 (slight migration) was observed in several animals in the 5x group on study days 56 and 70 and in one 3x female on study day 70. Only one animal was given a score of 2 (moderate migration). This was a male in the 5x group on study day 70, and while the material migrated, it did not actually drip off of the dog.

3. **Mortality**: One male puppy in the 1x group was euthanized moribund on study day 37. After a complete histopathological examination, a cause of death could not be determined. The puppy had previously been treated for coccidia but the parasite was not found at necropsy. The puppy had failed to thrive and lost weight despite supplemental nutritional support. All other puppies survived until the termination of the study.

B. **BODY WEIGHT AND WEIGHT GAIN**: Select mean body weight data are presented in Table 5. No treatment-related changes in mean body weight or body weight gain were observed. The body weight of treated puppies was slightly higher than controls, but this was not considered an adverse effect.

TABLE 5. Mean body weight (g ± S.D.) in puppies[a]

Day	Control	1x	3x	5x
Males				
0	2129 ± 431.2	2255 ± 274.2	2518 ± 578.0	2435 ± 449.1
21	2688 ± 650.9	2746 ± 861.1	3105 ± 936.2	3182 ± 581.7
42	3913 ± 756.5	3902 ± 868.7	4344 ± 1043.8	4342 ± 715.1
63	5283 ± 697.3	5432 ± 663.8	5411 ± 968.2	5611 ± 852.6
88	6805 ± 659.7	7108 ± 473.0	6956 ± 952.9	7212 ± 887.2
Females				
0	1716 ± 261.7	1994 ± 404.9	1941± 361.8	1944 ± 417.7
21	2139 ± 440.1	2842 ± 519.5	2358 ± 445.5	2445 ± 728.7
42	2974 ± 831.0	3863 ± 570.5	3224 ± 383.9	3297 ± 1014.0
63	4061 ± 762.1	5095 ± 637.6	4214 ± 463.9	4275 ± 903.4
88	5259 ± 730.0	6243 ± 761.9	5219 ± 524.4	5355 ± 807.5

[a]Data from Table 7, pp. 208-220 in MRID 48135309.

C. **FOOD CONSUMPTION:** No significant treatment-related findings were observed in any of the pups with food consumption. Throughout the study, the treated and control pups ate similar amounts. Select food consumption data are provided in Table 6.

TABLE 6. Mean food consumption (g/animal/day ± SD) in puppies[a]				
Week	Control	1x	3x	5x
Males				
3	182 ± 54.5	192 ± 60.4	172 ± 69.2	207 ± 10.6
6	206 ± 31.6	179 ± 46.0	194 ± 41.5	213 ± 14.8
9	219 ± 4.7	215 ± 3.7	210 ± 15.5	216 ± 3.4
12	281 ± 7.8	274 ± 5.7	259 ± 35.2	271 ± 4.9
Females				
3	164 ± 37.9	165 ± 35.3	169 ± 60.2	151 ± 60.5
6	151 ± 75.0	191 ± 31.3	168 ± 16.9	137 ± 47.3
9	187 ± 25.3	197 ± 27.8	188 ± 20.2	197 ± 28.7
12	218 ± 30.7	225 ± 37.8	202 ± 16.5	229 ± 49.8

[a]Data from Table 11, pp. 240-246 in MRID 48135309.

D. BLOOD ANALYSES:

1. **Hematology**: Occasional statistically significant differences were observed but they were minor and did not follow any type of dose response, indicating they were not treatment-related. No effects were observed on the measured coagulation parameters.

2. **Clinical chemistry**: Occasional statistically significant differences were observed in some clinical chemistry parameters, but all the changes were minor and none followed a dose response trend, indicating they were not treatment-related.

3. **Urinalysis:** There were no treatment-related findings observed in the urinalysis parameters evaluated.

E. PATHOLOGY RESULTS:

1. **Gross necropsy findings:** The male puppy that was euthanized moribund on study day 37 had wet matting of the hair coat, discoloration of the pancreas and thyroid, abnormal contents in the stomach and rectum and a small thymus. Some animals with angular deformity of the forelimb and enlargement of the carpal joint were randomly selected for a more thorough necropsy that involved evaluating the carpal joint, kidneys and thyroids/parathyroids. All had normal findings except for one male in the 3x group that had a slight varus deviation of the carpal joint.

2. **Histopathological findings:** In the puppy that was euthanized on study day 37, histopathological findings were consistent with decreased food intake and stress. The findings included reduced presence of zymogen granules in the exocrine pancreas, thymic lymphoid depletion and lymphoid hyperplasia of the ileum. The findings did not support a specific reason for death other than a failure to thrive. The carpal joints examined were normal histopathologically, and the radial epiphyses had normal proliferation and maturation of chondrocytes with normal progression and formation of primary and secondary spongiosa.

III. DISCUSSION and CONCLUSIONS

A. **INVESTIGATORS' CONCLUSIONS:** The study author concluded that the administration of Indoxacarb/Permethrin Topical Solution (SCH 900560) was well-tolerated in beagle puppies at 1, 3 and 5 times the recommended dose with 1x being defined as 15 mg Indoxacarb and 48 mg Permethrin per kg of body weight. No adverse test article-related effects were noted in either male or female beagle puppies as young as 8 weeks old at the proposed clinical (1x) dose every 4 weeks.

B. **REVIEWER COMMENTS:** The reviewer agrees with the study author that no adverse effects were observed in beagle puppies as young as 8 weeks old treated at the highest dose level. Treatment of the puppies had no effect on body weight, food consumption, clinical signs, clinical chemistry, hematology or urinalysis parameters measured, or gross and microscopic lesions. Although there were some statistically significant differences in some of these parameters, none exhibited a dose response trend or were consistent throughout the study. This companion animal safety study in beagle puppies is **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) with the stipulation that puppies must be 8 weeks of age or older and a dosage rate of no more than 0.1 mL/kg.

C. **STUDY DEFICIENCIES:** The study should have been conducted with a 1x dose level of at least 0.2 mL/kg, and the higher dosages should have been adjusted accordingly. Otherwise, the study has no major deficiencies and mostly followed the Companion Animal Safety Guideline (OPPTS 870.7200). The guideline recommends that animals should be acclimated for 2 weeks prior to the start of the study; these dogs were only acclimated for 7 days. However, this did not affect the integrity of the study.

1. **DP BARCODE:** 380196
2. **PC CODES:** 109701 (Permethrin); 067710 (Indoxacarb)
3. **CURRENT DATE:** May 20, 2011
4. **TEST MATERIAL:** SCH 900560, a pale, yellow liquid containing 43.48% w/w Permethrin and 13.77% w/w Indoxacarb.

Study/Species/Lab Study # / Date	MRID	Results	Tox. Cat.	Core Grade
Companion Animal Safety Study (dog)/adult beagles/Charles River Laboratories, Spencerville, OH 45887/Study No. JTG00005/January 15, 2010	48135308	Four groups (each 6M & 6F) of adult (~7 month old) dogs; Group 1 (placebo control) was treated with 0.5 mL/kg; Group 2 (1x) with 0.1 mL/kg SCH 900560; Group 3 (3x) with 0.3 mL/kg SCH 900560; and Group 4 with 0.5 mL/kg SCH 900560. Treatments were given on days 0, 14, 28, 42, 56 & 70. No treatment-related effects were observed. All dogs survived to termination. Study supports a 1x dosage rate of up to 0.1 mL/kg.	N/A	A (for dosage rate of 1 mL/kg)
Companion Animal Safety Study (dog)/ beagle puppies/ Charles River Laboratories, Spencerville, OH 45887/ Study No. JTG00004/January 15, 2010	48135309	Four groups (each 6M & 6F) of beagle puppies (~8 weeks old, M 1.6-3.4 kg; F 1.2-2.5 kg at start of study) ; Group 1 was treated with 0.5 mL/kg; Group 2 (1x) with 0.1 mL/kg SCH 900560; Group 3 (3x) with 0.3 mL/kg SCH 900560; and Group 4 with 0.5 mL/kg SCH 900560. Treatments were given on days 0, 14, 28, 42, 56 & 70. No treatment-related effects were observed. One male puppy in the 1x group on day 37 was laterally recumbent, cool to the touch with labored breathing, hemorrhagic feces and was euthanized moribund; cause of condition could not be determined. All other puppies survived to termination. No treatment-related effects were observed. Study supports a 1x dosage rate of up to 0.1 mL/kg.	N/A	A (for dosage rate of 1 mL/kg)

Core Grade Key: A = Acceptable, S = Supplementary, U = Unacceptable, W = Waived